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The Deterioration of Spatial Memory and the Role of the Masticatory Function during Aging: A Brief Literature Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

This article reviews the current state of scientific information on the relationship between the deterioration of spatial memory and the role of the masticatory function, both of which are primarily examined during the aging process. The article broadly examines the current notions regarding neuroscientific processing mechanisms of spatial memory. Additionally, some variables that produce alterations in hippocampal function during aging are presented here. Finally, the role that mastication fulfills as an emerging physiological mechanism of cognitive impairment compensation is discussed. This article concludes that, despite the recent progress in understanding the concepts presented in this article, evidence suggests that there are still many questions to be answered. These questions are sustaining the growing interest in the field of neuroscience in examining the underlying mechanisms of the intricate process of spatial orientation and their relation to masticatory function in aged organisms.

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1. INTRODUCTION

Technological advancements and their use in the prevention, treatment and curing of various diseases, along with an improvement in safety conditions, have increased life expectancy throughout the world [1]. It was found that the percentage of people aged over 60 increased from 8.1% in 1950 to 11% in 2010 and it is expected to reach 21.8% in 2050. In the most developed countries, this proportion is expected to increase from 21.7% in 2010 to 31.9% in 2050 [2]. It is projected that, globally, the number of elderly people will exceed the number young people for the first time in history in 2045. In the more developed regions, population aging is far advanced, thus causing the number of children to drop below that of older persons in 1998 [3].

Elderly people are able to adequately perform tasks which require less exertion of their memory mechanisms, as well as tasks which involve non-declarative or implicit memory, which only require repetition or recognition of a stimulus. Yet their performance decreases if they must remember specific information or perform actions without reminders. It was found that learning and retention while performing spatial tasks happens more slowly in elderly animals than in young and adult animals [4-6].

In terms of oral health, changes in oral tissue and oral functions, as well as secondary changes to extrinsic factors, often occur in older adults. These changes increase tooth loss due to periodontal disease, cavities, and lesions of the oral mucous, all of which result in an impairment of the masticatory function [7]. In recent years, the relationship between cognitive functions and the masticatory function has been the target of several investigations worldwide [8-12]. It has been found that an alteration of the masticatory function deteriorates the hippocampal-dependent cognitive processes by causing a loss of somatosensory stimulation of the oral cavity [13-16]. However, this relationship remains unclear and it is the subject of ongoing study [17,18]. This article will examine the concept of memory, specifically focusing on spatial memory, and it will explore the relationship between the deterioration of this memory function with the masticatory function within the framework of the aging process.

1.1 Spatial Memory

In general, two types of memory have been defined: the short-term memory and the long term memory. The latter can be further divided into implicit memory and explicit (or declarative) memory. Declarative memory can be even further divided into episodic memory and semantic memory [19]. Spatial memory is conceptualized as a subtype of episodic memory and it depends on the ability to remember something within a determined temporal and spatial context due to the information being stored within the framework of space-time [5]. Spatial memory is responsible for recognizing, encoding, storing, and retrieving information related to the arrangement of objects, specific routes, configurations, and spatial locations, thus allowing the organism to function in its environment [4].

1.2 Place Cells and Grid Cells

The concept of cognitive maps, which was developed in rodent experiments, allowed a better understanding of the underlying hippocampal processes in the mechanisms of spatial orientation [20]. In the hippocampus, some neurons have been identified that encode specific locations in an environment. These have been defined as place cells and they are found in rodents, nonhuman primates, humans, and also bats [20,21]. Place cells are neurons that are activated during the translational movement of an animal and they depend upon the location of the animal in a specific zone within an environment, independent of any particular stimulus or ongoing behavior [5]. These cells are typically pyramidal neurons located in the CA1 and CA3 hippocampal subfields and they are typically activated within a single area of a determined environment, namely the corresponding place field [22]. The size of a place field is related to the position of the place cells in the hippocampus on the septo-temporal axis (dorso-ventral). Those neurons that are found near the temporal zone have larger place fields [23].

It is hypothesized that the medial area of the entorhinal cortex (mEC) specializes in representing spatial information [24]. This hypothesis is due to a rather numerous cell type being identified in this area: grid cells [22,25]. These neurons are activated every time when

the animal's position coincides with any vertex of a regular grid of equilateral triangles covering the surface of an environment, finding that, just like in place cells, the activation pattern of grid cells increases along the dorsal-ventral axis of the mEC [25,26]. Empirical evidence has provided the hypothesis that the activation patterns of grid cells are the major determinant of place cell activation. This is due to the fact that grid cells are the most numerous cell type in the surface layers of the entorhinal cortex which are involved in spatial orientation and this structure is the main route of neocortical afferent information to the hippocampus [22,23]. Furthermore, in the entorhinal cortex the grid cells are interspersed with other cell types that would be involved in spatial orientation such as the head direction cells and border cells. It has been discovered that all of these cell types are projected directly from the entorhinal cortex into the dorsal hippocampus, suggesting that this would be the main source of spatial information that would activate place cells [24,25,27,28].

1.3 Aging of the Nervous System

Aging is a natural process in the life of an organism during which, despite modifications in biological processes, the organism must maintain its ability to adapt. This natural process is characterized by a set of changes responsible for the gradual deterioration of cells and organs which can make humans more vulnerable against the onset of disease and thus increase the possibility of death. During the natural aging of the nervous system, mild memory or cognitive deficits that affect the realization of complex activities can occur [29,30]. Among other changes, a decrease in the number and length of dendrites, fewer axons, and myelinated impairment, as well as significant synaptic loss with significant reduction in the volume and integrity of the white matter have been observed; furthermore, there is an increase in activated microglia, which over-express Interleukin 1 and have characteristics of phagocytic cells, but which are not accompanied by loss of other intellectual functions and do not limit self-sufficiency [30,31]. Aging results in a series of changes in social status, sensory perception, and cognitive and motor functions in individuals [7]. Human and rodent experiments have shown that there is a decline in spatial memory associated with aging and there is also evidence that aging is associated with a decrease in masticatory function [5,6,13,15,17].

1.4 Deterioration of Hippocampal Functions in Aging

Any reorganization related to memory and learning begins with synaptic plasticity (the changes in the structure or biochemistry of synapses that alter postsynaptic effects), which is induced in subsets of synapses and neurons where the release of neurotransmitters can reinforce or weaken these synapses [32,33]. The alteration of the mechanisms of hippocampal synaptic plasticity may be one of the causes of spatial deterioration that is observed in aging. In rodents, the spatial navigation paradigm (the Morris water maze) appears to be an appropriate model to evaluate such deficits, due to the fact that representations of the environment depend heavily on efficient hippocampal functioning, which appears to be impaired in the aging process in humans and animals [4,34].

One of the mechanisms of synaptic plasticity which underlie memory processes is long-term potentiation (LTP) [35-37]. It has been found that, in old age, memory impairment correlates with a decrease in late-phase LTP [38]. One of the molecules involved in this phase is the Brain-derived neurotrophic factor (BDNF), which has a central role in processing long-term memory. It has been found that a decrease in BDNF synthesis is associated with reduced formation of new synapses [34,37,39-41].

Elderly humans and animals have higher levels of corticosteroids than adult organisms [42]. Both the physiological and pharmacological actions of corticosteroids are mediated by their nuclear receptors, which are expressed ubiquitously and vitally in humans [43,44]. The feedback mechanisms that regulate corticosteroid levels deteriorate during aging, possibly due to a decrease of its receptors, resulting in increased circulating levels of the hormone [45]. Corticosteroids regulate hippocampal processes through their two nuclear receptors, the glucocorticoid receptor (type II receptor), a ubiquitous transcription factor that mediates most of the elements of response to glucocorticoids, and the mineralocorticoid receptor (type I receptor), which has a higher affinity for glucocorticoids and primarily mediates the functions that depend on low concentrations of the hormone [46]. The high concentration of corticosteroids alters long term potentiation in the hippocampus, thus deteriorating spatial memory which depends on said structure [47]. This

results in hippocampal atrophy and adverse effects on its functioning [45].

1.5 The Masticatory Function

Mastication is one of the primary functions of the stomatognathic system and is defined as the sum of the chewing cycles (one chewing cycle is each power stroke with start and end points in the position of maximum intercuspation) that are necessary to reduce food to an adequate size and form which makes it possible, through successive swallows, to consume fully. It involves a series of biological, neural, chemical, and evolutionary processes dependent on growth and development [16,48].

The neural stimulation that the masticatory function provides is only produced and received for about one hour per day (the total sum of chews in one day). During this hour of intense performance of masticatory activity, the different structures involved are used thoroughly. However, the quality of the action and the stimulation it produces through the neural pathways ultimately depend upon the nature of the food consumed [49].

Although chewing clearly influences cognitive functions such as memory, learning, and alertness, in addition to having an effect on arousal level and motor control [6,10,12,15,50], to date there is no consensus on the neural and humoral pathways connecting the oral cavity with the hippocampus [17,47]. However, it is understood that the sensory system of the trigeminal nerve transports sensitive information from the oral cavity to the central nervous system (CNS). The proprioceptive information of the masticatory function is transmitted to the CNS through both the trigeminal ganglion neurons and the mesencephalic nucleus neurons of the V cranial nerve. It has also been proposed that the involved humoral pathways are represented by various growth factors such as nerve growth and epidermal growth. These growth factors are produced, among other places, in the salivary glands and chewing increases their secretion. In conclusion, the effects of chewing on the CNS cannot be attributed to a single factor, but rather to multiple complex signals that are still being studied [16,17].

1.6 The Role of Mastication in Hippocampal-dependent Memory

Masticatory deprivation in diverse age groups of mice appears to primarily affect hippocampal function. Masticatory imbalances show a decrease in the number of neurons and an increase in the number of hypertrophic astrocytes. All of these changes seem to be exacerbated by aging and by the amount of time after tooth loss, which suggests additive effects [6].

Stress causes deterioration of spatial memory due to adrenal axis dysregulation, while chewing seems to alleviate this deficit. It was found that this activity increases corticosteroid receptors in the hippocampus, thus maintaining memory processes under severe stress conditions [47]. A disturbance in chewing caused by molar tooth loss over a long period of time can cause chronic stress that accelerates cognitive deterioration related to aging [18], also the corticosteroids decrease the effects of BDNF due to a decrease in the expression of its mRNA [51]. Additionally, in a study using rats it was found that masticatory function interference that was sustained for 10 days significantly decreased LTP in hippocampal CA1 neurons, while also increasing corticosteroids and plasma catecholamine [52].

It has been found that the sustained reduction of masticatory stimulation induced in mice by a powdered diet results in a loss of pyramidal cells in the CA1 and CA3 regions of the hippocampus [52]. Both of these regions are critical in the recognition of information in a spatial and temporal context given the connection between the two by the Schaffer collateral fibers [23,53]. It has been said that masticatory dysfunction caused by tooth extraction damages the neural cholinergic system in the hippocampus and parietal cortex, causing deterioration of spatial memory and reducing pyramidal cells in CA1, CA3 and CA4 [54-56]. In rats subjected to a powdered diet from weaning until their twelfth week of age, increased reactive oxygen species were found, thus contributing to the development of changes in the CNS by causing oxidative stress, especially in the hippocampus [57]. Additionally, stress related to the deterioration of chewing has been found to reduce the response of dopaminergic neurons in the hippocampus. Dopamine that reaches the hippocampal structure is projected from dopaminergic neurons of the ventral tegmental area of the midbrain and this pathway primarily regulates late phase LTP, which is related to long term memory [58].

The effect of mastication on spatial memory and on CA1 astrocytes has been evaluated. Scientists compared two groups of 18-month-old

mice which were divided based on the diet they received after weaning. In one group, deficient mastication was induced using a powder diet, while the other group had efficient mastication due to being fed a hard diet of pellets. The masticatory deprivation group showed a decrease in the number of neurons and an increase in the number of hypertrophic astrocytes, further demonstrating a decline in spatial memory when evaluated using the Morris Water Maze [6]. Another report assessed whether a stimulating environment and rehabilitation of masticatory function could reverse the decline in spatial learning and memory in 18-month-old mice. To mimic masticatory rehabilitation, the animals were fed a hard diet of pellets for six months followed by six months of a powdered diet and returning to hard diet of pellets for the last six months. These animals were compared to animals without rehabilitation that were fed a hard diet of pellets for 9 months followed by a powdered diet for nine months and with control animals who remained on the hard diet of pellets for all 18 months. The study concluded that the reduction in masticatory activity induced by administration of a powdered diet to sedentary mice (maintained in an unstimulated environment) impairs spatial learning and memory when evaluated in the Morris Water Maze. The rehabilitation of masticatory activity, regardless of the environment, recuperated memory loss and spatial learning, and a combination of a stimulating environment and masticatory rehabilitation significantly benefited the recuperation of spatial learning and memory in aged mice [10].

Based on multiple investigations and revisions made in previous years [59-63], the WHO has reported that tooth loss is a risk factor for Alzheimer's disease [64]. In experiments using rats with Alzheimer's, a decrease in dopamine release was found in the group of mice who also had masticatory deficiency induced by modifying their diet, as opposed to the group that was fed a solid diet. The findings of this investigation suggest that dopamine synthesis was not affected in the ventral tegmental area of the midbrain, but rather masticatory deficiency affected dopamine release in dopaminergic terminals in the hippocampus. Additionally, the results showed that memory and the ability to learn deteriorated in the group of mice with Alzheimer's and masticatory deficiency [65].

On the other hand, chewing can be considered as a form of exercise because it can increase both neuronal activity and cerebral blood flow [66]. Some authors have suggested that neurogenesis is regulated at the systemic level and that physical activity leads to increased neurogenic potential. It is possible that masticatory muscle activity during chewing could be sufficient to influence cell proliferation and neurogenesis [15,67].

2. CONCLUSION

Thanks to the discovery of several types of neurons in the last decade, most notably grid cell in the mEC, the understanding of processing spatial memory has been increased greatly; however, many questions remain to be answered about the inner workings of the structures involved in this type of memory. These questions support the growing interest that is developing in neuroscientific research on the underlying cellular, biochemical and genetic pathways in the intricate processing of spatial orientation and their relation to masticatory function during aging.

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CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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